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Is SII a predictive hematological parameter for subclinical inflammation of gestational diabetes mellitus?

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Abstract
Aim: In this study, we aimed to reveal the subclinical inflammation, which plays a role in the pathogenesis of Gestational Diabetes Mellitus (GDM), with the systemic immune-inflammatory index (SII), which is a new index created by formulating peripheral blood cells.
Material and Methods: This retrospective case-control study was conducted at a university hospital between June 2020 and July 2022. Between 24-28 weeks of gestation, 80 pregnant women with GDM, 240 healthy pregnant women and a total of 320 patients were included in the study.
Results: Women with GDM had higher age, gravidity, parity, body mass index (BMI) and birth weight. White bood cell (WBC), Neutrophil count (NC), Red cell distribution width (RDW), Platecrit (PCT), Neutrophil lymphocyte ratio (NLR) and SII values were significantly higher in the GDM group ($p<0.001$ for all parameters). There was no significant difference between the groups in hemoglobin value, Lymphocyte count (LC), platelet count (PC), Mean Platelet volume (MPV), Platelet distribution width (PDW), Platelet lymphocyte ratio (PLR) and high-sensitivity C- reactive protein (hsCRP) values. As a result, it was revealed that with a plasma SII >765.5 mg/dl, a successful prediction of GDM can be obtained with a sensitivity of 86.2% and a specificity of 80.6%.
Discussion: Plasma SII value was the highest predictive parameter in diagnosing GDM by analyzing simple blood count parameters. Each 1 unit increase in SII increased the risk of GDM 1.03 times in this study. New inflammatory parameter, called SII, have prognostic significance to determine the presence of GDM.

Keywords
Gestational Diabetes Mellitus, Novel Parameter, Systemic Immune-Inflammatory Index, Subclinical Inflammation

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Introduction

GDM is the most common pregnancy complication and has a multifactorial etiology. The incidence is higher in developed countries, where obesity and advanced-age pregnancies are more common [1]. The importance of GDM is that it is associated with perinatal complications such as macrosomia, shoulder dystocia, increased birth trauma, preterm birth, preeclampsia, increased primary cesarean section rate and neonatal outcomes such as neonatal hypoglycemia and respiratory distress syndrome. GDM is of great importance in pregnancy due to the emergence of obesity, hypertension, type 2 DM at later stages of life [2]. For these reasons, early detection and treatment of GDM ensure that possible complications can be prevented. Gestational diabetes occurs when pancreatic secretion is insufficient in maternal insulin resistance, which becomes evident with pregnancy. Endothelial dysfunction resulting from peripheral maternal insulin resistance and vascular damage caused by chronic low-grade inflammation is the main damage that plays a role in the pathophysiology of GDM. Inflammatory cytokines such as increased C-reactive protein (CRP), IL-6 and TNF-α are associated with type 2 and GDM. The pathophysiology of GDM has not been adequately clarified, although data on inflammation are available [3-6].

Studies conducted in recent years have demonstrated the presence of systemic inflammation with peripheral complete blood count parameters that are inexpensive, easy to obtain and apply. In these studies, it has been shown that neutrophils, lymphocytes and platelets originating from white blood cells are cells involved in inflammation [7]. Cell subtype ratios such as NLR, PLR and PCT levels reflect the presence of low-grade inflammation in novel markers such as mean MPV and systemic immune-inflammatory index (SII), which are relevant to chronic disease [8]. The systemic immune inflammatory index is a new inflammatory parameter derived from complete blood count (CBC) and is calculated using the following formula: peripheral neutrophil X platelet/ lymphocyte counts [9].

The aim of this study is to determine the importance of these parameters in predicting GDM by evaluating subclinical inflammation, which plays a role in the pathogenesis of GDM, with SII created by complete blood count parameters and modification.

Material and Methods

The study was designed as a retrospective case-control study in a University Hospital Perinatology Clinic between July 2020 and September 2022. The original study was approved by Saglik Bilimleri University, Bursa Yuksek Ihtisas Research and Training Hospital Ethics Committee with protocol number (2011-KAEK-25 2020/07-09). Patient age, parity, gestational age and birth weight were reviewed retrospectively from the hospital database. The study was carried out with 80 patients aged 18-45 years with newly diagnosed GDM and 240 healthy patients without GDM diagnosis a total of 320 pregnant women. Chronic connective tissue patients such as multiple pregnancies, congenital anomalies, primary essential HT, preeclampsia, eclampsia, pre-gestational DM, pregnant women with thyroid function disorders, rheumatoid arthritis, vasculitis were excluded from the study. GDM diagnosis at 24-28 weeks was performed by a two-step 75 g glucose challenge test in accordance with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. The diagnosis of GDM was established when any single threshold value was met or exceeded (fasting value glucose levels > 5.1 mmol/L [92 mg/dl], 1-hour plasma glucose levels of >10 mmol/L [180 mg/dl], and two-hour plasma levels of > 8.5 mmol/L [153 mg/dl].

The peripheral blood samples were analyzed in the hematology laboratory of the hospital, using the automated Beckman Coulter LH 780 Analyzer. Hemoglobin (Hb), RBC, WBC, PC, MPV, PDW, PCT, NC and LC values were measured.

Statistical analyses

Statistical analyses were performed using SPSS windows version 22 software (SPSS Inc.). The Kolmogorov–Smirnov normality test was run for checking the distribution of CBC, and the Levene statistic test was used to test the homogeneity of variances. Unpaired Student's t-test was conducted for comparison of normally distributed variables. The results of normally distributed variables are presented as mean ± standard deviation (SD). The Mann–Whitney U test was used for the comparison of non-normally distrusted hematological parameters, and the results were expressed as median values. A p-value <0.05 was considered statistically significant. Receiver operating characteristic curves (ROC) were used to evaluate the predictive value of SII in GDM prediction, and the area under the curve (AUC) determined the discriminative ability of GDM.

Results

A total of 320 participants were included in this study. There were 80 patients in the GDM group and 240 healthy pregnant women in the control group. Women with GDM had higher age, gravidity, parity, BMI and birth weight (p<0.001). 1. and 5. Apgar scores were higher in the control group (p<0.001). There was no difference between the two groups in terms of gestational week length. Demographic and clinical data of study groups are shown in Table 1.

WBC, NC, RDW, PCT, NLR and SII variables were significantly

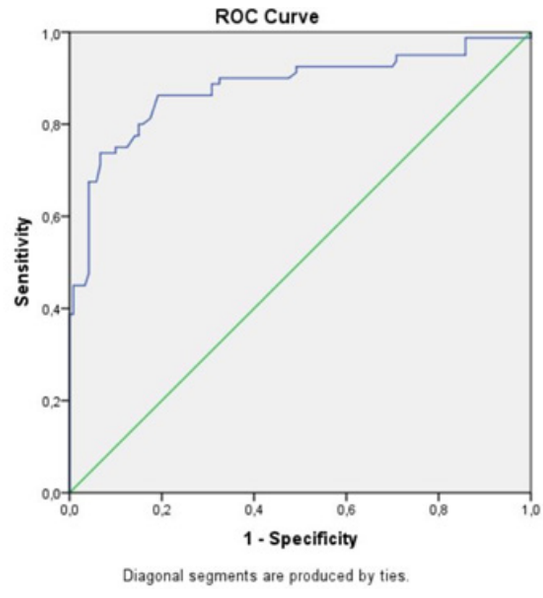

Figure 1. ROC analysis chart in terms of plasma SII cut-off value in the prediction of GDM.

Table 1. Sociodemographic and perinatal characteristics of the study groups.

Variables	Group	n	X±SD/Median (min-max)	p
Age (yr)	Control	240	28,88 +-5,83	<0.001
	GDM	80	31,88+-5,67	
Gravidity (n)	Control	240	2 (2-3)	<0.001
	GDM	80	3 (2-4)	
Parity (n)	Control	240	1(1-2)	<0.001
	GDM	80	2 (1-3)	
BMI (kg/m2) *	Control	240	24.52 ± 1.47	<0.001
	GDM	80	27.01 ± 2.19	
Pregnancy length # (wk)	Control	240	39 (38–40)	0.013
	GDM	80	38 (38–39)	
Birth weight (gr) *	Control	240	3189 (2775–3300)	<0.001
	GDM	80	3400(3145-3950)	
1 APGAR score*	Control	240	9(9-9)	<0.001
	GDM	80	9(8-9)	
5 APGAR score*	Control	240	10(10-10)	<0.001
	GDM	80	10(9-10)	

BMI: Body mass index, SD: standard deviation, X: mean, min: minimum, max: maximum. #; Descriptive analyses were presented using median (min-max), *; for non-normally distributed variables. Student's t-test *p<0.05 and the Mann-Whitney U test#were used for the comparison of the groups. p<0.05 was considered significant.

Table 2. Comparison of laboratory parameters with groups.

Laboratory Parameters	GDM diagnosis (n=80) X±SD/Median (min-max)	Healthy group (n=240) X±SD/Median (min-max)	p
Hemoglobin (gr/dl) #	11.4 (7.2-19.3)	11 (7.1-14.3)	0.019
White blood cell# (10^9/L)	11.9 (5.9-22)	11.2 (5.9-24)	<0.001
Neutrophil# (10^9/L)	6.1±1.7	5.8±1.6	<0.001
Lymphocyte# (10^9/L)	1.7 (0.3-3.2)	1.7 (0.5-7.6)	0.83
Mean platelet volume*(fL)	10.4 ± 0.1	9.4 ± 0.1	0.063
Platelet distribution width# (%)	16.6 (11.9-18.1)	16.5 (6.2-17.1)	0.181
Plateletcrit# (%)	0.22 (0.14-0.35)	0.18 (0.12-0.30)	<0.001
Red cell distribution width#(%)	15.5. (12.9-22.1)	14.2 (11.5-17)	<0.001
Platelets*(10^9/L)	242.1 ± 8.7	238.9 ± 6.1	0.61
Neutrophil/Lymphocyte ratio#	6.1 (2.1-38)	4.56 (1.2-22.4)	<0.001
Platelet/Lymphocyte ratio#	152.1 (20.4-549)	136.9 (26.2-482)	0.57
CRP [mg/L]	9.2 (4.7–19.2)	6.7 (3.5–10.6)	0.092
SII [mg/dl]	856. ±348.6	658.3±205.8	<0.001

SD: standard deviation, X: mean, min: minimum, max: maximum. Descriptive analyzes are presented using (X ± SD), median (min-max), for normally distributed variables and, non-normally distributed variables, respectively. Student's t-test *p<0.05 and Mann-Whitney U test #p<0.05 were considered significant.

higher in the GDM group than in the control group (p<0.001 for all parameters). In laboratory findings, there was no significant difference between the groups in hemoglobin value, LC, PC, MPV, PDW, PLR and hs-CRP values. Comparison of laboratory parameters between the groups is given in Table 2.

The plasma SII value was the highest predictor of GDM diagnosis by analyzing blood parameters. Each 1 unit elevation of the SII increases the risk of GDM by 1.03 times (p<0.001)

Using the ROC (receiver operating characteristics) curve, we analyzed the chance of predicting GDM of pregnancy with the plasma SII. We determined a cut-off value for the plasma SII. According to the ROC curve and the area under the curve table (AUC), the SII had a diagnostic value in predicting GDM (p<0.001). As a result, if the plasma SII >765.5 mg/dl, a successful prediction can be obtained with 86.2% sensitivity and 80.6% specificity (Figure 1).

Discussion

Changes occur in the regulated balance between pro- and anti-inflammatory states in pregnancy compared to the non-pregnant state. This intertwined inflammatory process provides the extravillous trophoblast invasion and placentation necessary for normal implantation. The excessive and exaggerated response in this process plays a role in the pathogenesis of GDM [10]. Whole blood cell indices are widely used, practical and cost-effective markers that have been used in various fields of medicine for years and provide important data on many diseases. In various studies, it has been shown that platelet indices such as MPV, PDW, PCT, fibrinogen and coagulation factors as inflammatory markers and indices such as PLR and NLR are affected in GDM patients [11]. Neutrophils, which make up most of the white blood cells, form the first line of defense in inflammation and provide active nonspecific inflammation in immune defense. While neutrophils are one of the most important effectors in acute inflammation, they also contribute to chronic inflammatory conditions and adaptive immune responses. Lymphocytes, platelets and monocytes play a role in the modulation of the inflammatory process, and this process results in an increase in NLR. Platelets promote the initiation of the inflammation cascade and modulate immune functions by expressing several pro-and anti-inflammatory molecules [12]. In recent years, in studies using NLR and PLR as inflammation biomarkers in GDM, both NLR and PLR levels were found to be significantly higher [13]. In the study by Yılmaz et al., mean NLR level was found to be significantly higher in pregnant women with GDM [14]. Although the pathophysiology of the increase in MPV in GDM has not been fully explained, it has been shown that insulin resistance is the main descriptor of platelet activation. Inflammatory cytokines such as hs-CRP, IL-6 and TNF-a have been observed to increase in the circulation in GDM. These cytokines create local, central and peripheral effects on different tissue types [15]. Due to increased hyperglycemia in GDM, platelets swell due to osmotic pressure, resulting in larger platelet production than magakaryocytes. The increase in MPV level in GDM has been shown in many studies. In the study by Sahbaz et al., PCT, MPV and PDW were found to be statistically significantly higher in GDM patients [16]. In the study by Aytan et al., RDW and NRBC were found to be significantly increased in GDM patients, but there was no difference in platelet markers [17]. Similarly, in our study, PCT and RDW were found to be significantly higher in the GDM group. This increase in MPV and PDW was not statistically significant. Hs-CRP, one of the inflammation markers, is widely used for the evaluation and treatment of inflammation. In a prospective study, hs-CRP was found to be high in correlation with increased maternal glucose level and BMI [18]. Kirbas et al. in their study using CRP as an inflammation marker, found that non-obes women with a CRP > or = 5.3 in GDM patients had a 3.7-fold increased risk of GDM. However, in our study, although hs-CRP values were higher in GDM, there was no significant difference compared to the control group (9.2+-6.4) (6.7+-2.3) [19].

The first studies using the systemic inflammatory index in the literature were studies assessing the prognosis of solid tumors such as hepatocellular and colorectal cancer and patients with coronary heart disease [20]. Lymphocytes, neutrophils and platelets, which are components of the SII formula, are involved in inflammation, while SII is also a combination of PLR and NLR. The inclusion of these blood cells in the formula is he best indicator of inflammation. Although many studies have investigated complete blood count parameters to predict adverse pregnancy outcomes, there are not enough studies using SII as a marker. Tanacan et al. has shown that SII and platelet counts can be useful in predicting this adverse outcome in pregnancies complicated by preterm premature rupture of the membranes [21]. Akdulum et al. in their study predicted that increased SII in first trimester pregnancies could predict GDM and stated the cut off value as 607.02. In our study, we found an SSI >765.5 mg/dl, with a significantly higher cut-off value in GDM patients, which supports the result of this study. We found that each unit height in SII increased the risk of GDM 1.03 times. The increase in this inflammation parameter is a result of the altered immune response of blood cells to physical stress in GDM at 24-28 weeks of gestation.

Conclusion

This study, we found a relationship between subclinical inflammation in the pathogenesis of GDM and SII. This index, calculated with a simple hemogram parameter can be used to predict GDM at 24-28 weeks of pregnancy. Thus, the early diagnosis of GDM with a simple, easily obtained and inexpensive inflammatory hematological parameter enables the continuation of the relevant programs and planning to predict the set goal.

There are some limitations in our study. It was a retrospective, single-center study with a relatively small sample size.Therefore, it is necessary to apply the findings to the general population in studies with a larger number of patient.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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